REMARKS

The term "turobuterol" has been replaced with the term --tulobuterol-- throughout the specification, abstract and claims. In the original PCT application of the present application, only "ツロブテロール" in Japanese is used. The correct English name of Japanese "ツロブテロール" is "tulobuterol", as shown in the Japanese medical commentary, enclosed herewith. Additionally, the front page of WO 2004/112770 also shows that the correct English translation of the above Japanese term is "tulobuterol". A copy of the front page of WO '770 is enclosed. It is therefore submitted that no new matter has been added to the application.

A marked-up copy of the specification and abstract, indicating the changes made therein, is enclosed herewith.

Respectfully submitted,

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直ちに中止し適切な処置を行う ㋐ショック(頻度不明):ショックを起こすことがあるので，観察を十分に行い，異常が認められた場合には，直ちに中止し適切な処置を行う ㋒血圧下降(0.1～5%未満):血圧下降等の循環障害を起こすことがある

ⓑその他の副作用

種類\頻度	頻度不明
過敏症(注)	じんま疹等

(注)このような症状が現れた場合には中止する

❻高齢者への投与:一般に高齢者では生理機能が低下しているので減量するなど注意する **❼妊婦，産婦，授乳婦等への投与** ⓐ妊婦又は妊娠している可能性のある婦人には治療上の有益性が危険性を上回ると判断される場合にだけ投与する［妊娠中の投与に関する安全性は確立していない］ ⓑ分娩の際は必要最小量を投与する［胎盤を通過するという報告がある］ **❽その他の注意**:動物実験においてカルシウム拮抗剤による非脱分極性筋弛緩剤の筋弛緩作用の増強が認められたとの報告があるので，カルシウム拮抗剤を長期間にわたって投与されている患者に投与する場合は慎重に投与する **❾室温・遮光保存** **❿規制等**:塩化ツボクラリン・塩化ツボクラリン注射液㊀㊁㊂

作用 **❶薬物動態**(参考):ヒト及び一部動物実験での体内における消長は，静注直後血漿中にひろがり，第1相で速やかに血漿から細胞外液に拡散し，一部分は終板に結合し，注射直後に上昇した血中濃度は5～6分の半減期で急速に低下。この際一部分は血漿タンパクと結合。次いで第2相では体組織や水分への再分布が起こり，同時にある程度分解及び腎から排泄。この時期には血中濃度は半減期45分で徐々に低下，2～3時間後には約1/3は尿中に排泄。第3相は主として分解と排泄の時期で，半減期約3.5時間で血中濃度は更にゆっくりした経過をとって低下 **❷薬効薬理** ⓐヒトに静注後，筋弛緩はまず眼瞼下垂，複視に次いで，咽喉，頸部，体幹，四肢，横隔膜の順に進行，回復時にはこれと逆過程。通常2～3分後に効果発現，25～30分持続 ⓑ作用機序は非脱分極性，神経筋接合部でアセチルコリンと競合し，脱分極を妨げることによる

気管支拡張β_2-刺激剤 225

ツロブテロール
tulobuterol (JAN)

添付文書 ホクナリンの内服・エアゾール1998年8月改訂，テープ1998年10月改訂

製品

セキナリン *Sekinarin* 錠1 mg ドライシロップ0.1%(分包0.5 g)(東和薬品)

ツロブリン *Turobrin* 錠1 mg ドライシロップ0.1%(分包0.5 g)(大原薬品，一模範薬品)

ベラチン *Berachin* 錠1 mg ドライシロップ0.1%(分包0.5 g)(三菱東京)

ホクナリン *Hokunalin* 錠1 mg ドライシロップ0.1%(分包0.5 g) エアゾール0.5922%(5 mL) テープ0.5・1・2 mg(北陸，一マルホ)

組成 錠:1錠中塩酸塩1 mg

ドライシロップ:塩酸塩0.1%

エアゾール:1容器(5 mL)，1 g中5.922 mg。1回噴霧量0.4 mg

テープ:1枚(2.5 cm²)中0.5 mg，(5 cm²)中1 mg，(10 cm²)中2 mg

ツロブテロールは白色の結晶又は結晶性の粉末で，においはない。メタノール又はクロロホルムに極めて溶けやすく，エタノール，氷酢酸，エーテル又はイソプロピルエーテルに溶けやすく，ヘキサンにやや溶けにくく，水にほとんど溶けない。旋光性がない。融点:90～93°C

塩酸ツロブテロール tulobuterol hydrochloride (JP)は白色の結晶又は結晶性の粉末である。メタノールに極めて溶けやすく，水，エタノール又は氷酢酸に溶けやすく，無水酢酸にやや溶けにくく，エーテルに極めて溶けにくい。水溶液(1→20)は旋光性を示さない。融点:約163°C

適応 内:次の疾患の気道閉塞性障害に基づく呼吸困難など諸症状の緩解:気管支喘息，急性気管支炎，慢性気管支炎，喘息性気管支炎，肺気腫，けい肺症，塵肺症

エアゾール:次の疾患の気道閉塞性障害に基づく諸症状の緩解:気管支喘息。適応関連注意:喘息発作に対する対症療法剤であるので使用は発作発現時に限る

テープ:次の疾患の気道閉塞性障害に基づく呼吸困難など諸症状の緩解:気管支喘息，急性気管支炎，慢性気管支炎，肺気腫

用法 内:塩酸ツロブテロールとして1回1 mg，1日2回(増減)，小児にはドライシロップを1日0.04 mg/kg(標準投与量15～9歳1～2 mg，8～3歳0.5～1 mg，2歳～6カ月0.25～0.5 mg)を2回に分服(増減)

エアゾール:ツロブテロールとして1回0.8 mg(2吸入)(増減)。用法関連注意:患者に対し，過度の使用により，不整脈，心停止等の重篤な副作用が発現する危険性があることを理解させ，次の事項及びその他必要と考えられる注意を与える ①成人1回2吸入の用法・用量を守り，1日4回(原則として成人8吸入)までとする ②発作が重篤で吸入投与の効果が不十分な場合には，可及的速やかに医療機関を受診し治療を求める

テープ:ツロブテロールとして1日1回2 mg，小児には9歳以上2 mg，8～3歳1 mg，2～0.5歳0.5 mgを胸部，背部又は上腕のいずれかに貼付

注意 内:**❶禁忌**:本剤の成分に対し過敏症の既往歴のある患者 **❷慎重投与** ⓐ甲状腺機能亢進症の患者［症状が増悪するおそれがある］ ⓑ高血圧症の患者［血圧が上昇することがある］ ⓒ心疾患のある患者［心悸亢進，不整脈等が現れることがある］ ⓓ糖尿病の患者［糖代謝が亢進し，血中グルコースが増加するおそれがある］ ⓔ高齢者［高齢者への投与の項参照］ **❸重要な基本的注意** ⓐ用法・用量どおり正しく使用しても効果が認められない場合には，本剤が適当でないと考えられるので中止する。なお，小児に投与する場合には，使用法を正しく指導し，経過の観察を十分に行う ⓑ過度に使用を続けた場合，不整脈，場合によっては心停止を起こすおそれがあるので，使用が過度にならないように注意する

❹相互作用

併用注意

薬剤名等	臨床症状・措置方法	機序・危険因子
カテコールアミン製剤 ・エピネフリン ・イソプレナリン等	臨床症状:不整脈，場合によっては心停止を起こすおそれがある	機序:本剤及びカテコールアミン製剤は共に交感神経刺激作用を持つ
キサンチン誘導体 ・テオフィリン ・アミノフィリン ・ジプロフィリン等	臨床症状:低カリウム血症による不整脈を起こすおそれがある	機序:本剤及びキサンチン誘導体は共に細胞内へのカリウム移行作用を持つ
ステロイド剤 ・プレドニゾロン ・ベタメタゾン ・ヒドロコルチゾン等 利尿剤 ・トリクロルメチアジド ・フロセミド ・アセタゾラミド等	臨床症状:低カリウム血症による不整脈を起こすおそれがある	機序:ステロイド剤及び利尿剤は尿中へのカリウム排泄を増加させる

❺副作用:承認時における安全性評価対象例1,572例中，副作用は199例(12.66%)，278件(17.68%)に認められ，その主なものは振戦102件(6.49%)，心悸亢進89件(5.66%)であった。また，本剤に起因すると考えられる臨床検査値の異常変動は認められなかった。再審査終了時における安全性評価対象例21,986例中，副作用は505例(2.30%)，727件(3.31%)に認められ，その主なもの

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WO 2004/112770 A1

(54) Title: ADHESIVE PATCH CONTAINING TULOBUTEROL

(54) 発明の名称: ツロブテロール含有貼付剤

(57) Abstract: An adhesive patch which comprises a substrate and, superposed thereon, a pressure-sensitive adhesive layer comprising a rubber, a tackifier resin, and a softener, wherein the pressure-sensitive adhesive layer contains tulobuterol as an active ingredient in a concentration as low as 1 to 4 wt.% in a dissolved state and further contains a higher fatty acid as a release control agent in an amount of 0.1 to 3 wt.%. The adhesive patch contains tulobuterol in a low concentration and has the ability to stably control the release.

(57) 要約: 支持体上にゴム、粘着付与樹脂および軟化剤からなる粘着剤層が積層された貼付剤であって、その粘着剤層に有効成分としてツロブテロールを１～４重量%の低濃度溶解状態で含有し、放出制御剤として高級脂肪酸を０.１～３重量%配合したツロブテロールを低濃度に含有し安定な放出制御能を有する貼付剤。

Version with Markings to Show Changes Made

SPECIFICATION

PATCHES CONTAINING ~~TUROBUTEROL~~TULOBUTEROL

TECHNICAL FIELD

The present invention relates to a dermally absorbable type patch containing ~~turobuterol~~tulobuterol.

BACKGROUND ART

Various dermally absorbable type preparations containing ~~turobuterol~~tulobuterol have been recently proposed as preparations making up the demerits of the oral preparation containing ~~turobuterol~~tulobuterol (See Japanese Patent Publication A 11-228395, Japanese Patent No. 2753800 (Japanese Patent Publication A 7-285854), WO 97/14411 and Japanese Patent No. 2633089 (Japanese Patent Publication A 5-194202)).

A patch prepared by dissolving ~~turobuterol~~tulobuterol into an adhesive has such a demerit as the duration necessary to sustain its effective serum concentration is not attained.

Therefore, techniques to increase the concentration of ~~turobuterol~~tulobuterol or to contain much amount of it by thickening an adhesive layer have been tried.

For example, in Japanese Patent Publication A 11-228395, a ~~turobuterol~~tulobuterol-patch which has a structure to fully dissolve ~~turobuterol~~tulobuterol are proposed. However, when such a patch is preserved for a long time due to the high concentration of ~~turobuterol~~tulobuterol, the preparation is apt to receive the influence by changes of circumstances such as temperature, etc. For example, even if the preparation has a good quality just after preparing it, with the passage of time there is a possibility that drug-release pattern becomes different

from one at the earlier time because ~~turobuterol~~tulobuterol crystallizes in the adhesive layer or changes of the concentration occurs.

In general essential physical properties such as adhesivity and shape retention of a patch is broken down and it is impossible to stably release the drug when a large amount of ingredients, which are either essential or unessential, are contained in the patch.

In regard to a patch containing much amount of ~~turobuterol~~tulobuterol, when the amount of an adhesive is too much, the essential physical properties becomes worse and during application of the patch, it gives an uncomfortable feeling to a patient and there is also a possibility to drop it out due to rubbing with clothes.

Further, in regard to a patch in which ~~turobuterol~~tulobuterol is much dissolved in the higher concentration, it can not help containing much amount of ~~turobuterol~~tulobuterol and therefore, it is neither economical nor practical.

On the other hand, a patch in which both soluble type ~~turobuterol~~tulobuterol and crystalline type ~~turobuterol~~tulobuterol are contained in the specific rates (see Japanese Patent No. 2753800), a patch prepared by recrystallizing ~~turobuterol~~tulobuterol in an adhesive (see WO97/14411), a patch consisting of ~~turobuterol~~tulobuterol and a specific co-polymer, wherein ~~turobuterol~~tulobuterol is suspended or microcapsulized and they are included in the adhesive layer, or a patch prepared by constructing matrix layers, adhesive layers or reservoir layers, and by laminating theses layers (see Japanese Patent No. 2633089), etc., were proposed as a dermally absorbable type patch which is aimed for a long lasting preparation of ~~turobuterol~~tulobuterol.

However, in regard to these patches, when they are preserved for long time, they are apt to receive the influence by changes of circumstances such as temperature, etc. For example, owing to the temperature rising in

summer, ~~turobuterol~~tulobuterol in crystals, suspensions or microcapsules contained in the patch dissolves and on the contrary, owing to the temperature dropping in winter, the dissolved ~~turobuterol~~tulobuterol begins to crystallize. Also in case of laminated type preparations, owing to changes of circumstances, movement (transfer) of ingredients such as ~~turobuterol~~tulobuterol and other ingredients occurs between matrix laminated layers and reservoir-layers, and the release pattern of ~~turobuterol~~tulobuterol from the patch is changed and there is a possibility to give the influence to the therapeutic effect of ~~turobuterol~~tulobuterol.

As well, these patches require complex techniques for suspending ~~turobuterol~~tulobuterol, microcupsulation of it and stable blending it into the matrix, and selection of the condition for recrystalization of it in the matrix, construction of the matrix and the reservoir layer, laminating, etc. They are problematic.

DISCLOSURE OF INVENTION

The object of the present invention is to provide a patch in which ~~turobuterol~~tulobuterol is contained in the lower concentration, but the patch has controllability of stable drug-release.

The present inventors have been extensively studied in consideration of the above problems and as a result, have found that a patch prepared by containing ~~turobuterol~~tulobuterol in the lower concentration in an adhesive layer which was prepared by suitably combining a higher fatty acid, a rubber, an adhesive resin and a plasticizer, shows unexpectedly the drug-release in therapeutically effective amount and an ability to easily control drug-releasing pattern, is hardly influenced by changes of the passage with time and furthermore, has essential physical properties such as adhesivity and shape pretension which are adjustable, and the process for preparation thereof is simple. Thus the present invention has been completed.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows changes of a passage with time of ~~turobuterol~~tulobuterol-serum concentration in case of applying patches of Example 1 and Comparative example 1.

Figure 2 shows changes of the passage with time of ~~turobuterol~~tulobuterol-permeability on extracted rat-skin in case of applying patches of Example 1, Comparative example 2 and Comparative example 3.

Figure 3 shows changes of the passage with time of ~~turobuterol~~tulobuterol-permeability on extracted rat-skin in case of applying patches of Example 1, Comparative example 1, Comparative example 4 and Comparative example 6.

Figure 4 shows changes of the passage with time of ~~turobuterol~~tulobuterol-permeability on extracted rat-skin in case of applying patches of Example 4 and Comparative example 5.

BEST MODE FOR CARRYING OUT THE INVENTION

Namely, the present invention relates to a patch containing ~~turobuterol~~tulobuterol prepared by laminating an adhesive layer consisting of a rubber, an adhesive resin and a plasticizer on a backing, wherein 1 to 4 w/w % of ~~turobuterol~~tulobuterol as an active ingredient and 0.1 to 3 w/w % of a higher fatty acid, preferably C11-22 fatty acid, especially preferably C14-18 fatty acid as a drug-release controlling agent are contained in the said adhesive layer.

The present invention also relates to a patch containing ~~turobuterol~~tulobuterol, wherein 5 to 35 w/w % of the rubber, 20 to 70 w/w % of the adhesive resin and 5 to 60 w/w % of the plasticizer are contained in the above adhesive layer.

In regard to patches containing ~~turobuterol~~tulobuterol which have

been traditionally proposed, it has been considered that it is essential to blend an acrylic adhesive which has a large polar or reactive group, or an adhesive resin having a large polarity such as a rosin in an adhesive layer.

However the patch related to the present invention does not need such substances, and that it is found that to blend such substances in an adhesive layer is not rather preferable because such substances cause to give great influences to release pattern of ~~turobuterol~~tulobuterol and stability in changes of the passage with time.

The constitution of the patch preparation of the present invention is illustratively explained below.

~~Turobuterol~~Tulobuterol which is contained as an active ingredient in the preparation of the present invention is dermally absorbed and exhibits an effect as a bronchodilator, and the preparation is characterized in containing ~~turobuterol~~tulobuterol in its small amount of 1~4 w/w %. When the amount is less than 1 %, the area of application must be broadened in order to make the therapeutic effects exhibit. When the amount is beyond 4 w/w %, it is necessary to admix other ingredients to control the drug-release because the concentration of the drug becomes high and the drug is contained much. And as a result, there is a possibility to break down essential physical properties as a patch. These amounts therefore, are not preferable.

The higher fatty acid admixed in the present preparation has an activity to stably control release pattern of ~~turobuterol~~tulobuterol, and is used for the drug-release controlling agent. The higher fatty acid includes C_{11-22}, preferably C_{14-18} fatty acid, such as linolic acid, linolenic acid, oleic acid, stearic acid, palmitic acid, lauric acid, myristic acid, isostearic acid, ricinolic acid, etc., especially preferably oleic acid and stearic acid.

The amount is 0.1~3 w/w %, preferably 0.2~2 w/w %, more preferably 0.3~1 w/w %. When the amount is less than 0.1 w/w %,

~~turobuterol~~tulobuterol is quickly released, and when the amount is beyond 3 w/w %, the drug-release is excessively controlled. Therefore these amounts are not preferable.

The rubber admixed in the present preparation has an ability to control the strength of an adhesive. The rubber includes a natural rubber, a synthetic rubber, such as isoprene rubber, styrene-butadiene rubber, styrene·butadiene block copolymer, styrene·isoprene block copolymer, preferably a synthetic rubber from the viewpoint of quality, especially preferably styrene·isoprene block copolymer.

The amount is usually 5~35 w/w %, preferably 10~30 w/w %, especially preferably 15~25 w/w %. When the amount is less than 5 w/w %, the strength of the adhesive does not become enough, and when the amount is beyond 35 w/w %, the strength becomes too high and the sticking power decreases.

The adhesive agent admixed in the present preparation has an ability to control the adhesive strength of an adhesive. The adhesive agent includes petroleum resin, polyterpene resin, polyolefin resin, saturated alicyclic hydrocarbon resin, etc., especially preferably petroleum resin, and saturated alicyclic hydrocarbon resin.

The amount is usually 20~70 w/w %, preferably 30~60 w/w %, especially preferably 40~55 w/w %. When the amount is less than 20 %, the adhesivity of the adhesive agent does not become enough, and when the amount is beyond 70 w/w %, the sticking power becomes too high. Therefore, these amounts are not preferable.

The plasticizer admixed in the present preparation has an ability to control the viscosity of the adhesive and is used to delicately control essential physical properties, such as sticking power, strength and improvement of sensibility. The plasticizer includes a liquid resin, an oil, liquid paraffin, polybutene, etc., especially preferably liquid paraffin and

polybutene.

The amount is usually 5~60 w/w %, in accordance with the amounts of a rubber and an adhesive agent contained.

The preparation of the present invention is prepared by wrapping the adhesive layer having the above mentioned constituents with both a backing and a release liner. The weight of the adhesive layer is 20~200g/m^2, preferably 50~150 g/m^2. When the weight is less than 20g/m^2, the sticking power becomes very weak and when the weight is beyond 200g/m^2, the sticking power becomes excessively strong and therefore, there is a possibility to injure the applied skin. Furthermore, to increase the weight without any object is not preferable from the economical viewpoint.

The backing is not limited as long as it is usually used and thereon an adhesive can be extended. However, a preferable backing is one that does not give excessively undesirable feeling to the skin during application and fully keep the adhesive in order not to remain on the skin when releasing off. Also the preferable backing is one which does not absorb ~~turobuterol~~tulobuterol, such a polyester film as polyethyleneterephthalate (PET), a polypropylene film, and paper, a fabric, or an unwoven fabric laminated on thereon.

The liner is preferable one which does not absorb ~~turobuterol~~tulobuterol, such a polyester film as polyethyleneterephthalate (PET) etc., or its laminated film. The liner is preferable easily releasable from an adhesive when it is released. If necessary, a release agent such as silicon resin may be spread on the adhesive surface of the liner.

The suitable method for preparing the present preparation is a dry method. For example, constituents of an adhesive are dissolved in an organic solvent and the resulting solution is uniformly spread out on the one side of the liner. The treated liner is dried to remove the solvent and is stuck on the backing. Thus prepared patch is cut in a suitable size to be

packed in a sealed package.

A hot-melt method as another method is considered. Namely the constitutions of an adhesive are blended and melted at about 100~200°C and then, spread on the liner at the same temperature. The preparation is cooled to prepare a patch.

This method has a merit in the viewpoint not to use an organic solvent, but the constituents are denatured to some extent as the heat charge is very large. Therefore, essential physical properties and the release pattern of ~~turobuterol~~tulobuterol, etc., becomes unstable and the high processing technique is necessary for preparing it. Therefore, this method can not be chosen as the first option from the practical viewpoint.

Example

The present invention is explained by illustrating examples and test-examples, but the present invention is not limited by these examples.

Example 1

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	2
Oleic acid	0.5
Styrene·isoprene· styrene block copolymer	20
Saturated alicyclic hydrocarbon (Petroleum resin)	48
Polybutene	10
Liquid paraffin	19
Dibutylhydroxytoluene	0.5
Weight of adhesive	100g/m^2
Backing	PET 10μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, ~~turobuterol~~tulobuterol and oleic acid were dissolved in a suitable amount of toluene (Solution A). On the other hand, styrene·isoprene·styrene block copolymer, saturated alicyclic hydrocarbon resin, polybutene, liquid paraffin and dibutylhydroxytoluene were mixed with a suitable amount of toluene until being homogenous (Mixture B).

The solution A and the mixture B were stirred until being homogenous, and the mixture was spread on the release coated surface of the polyethyleneterephthalate (PET) liner in the amount of 100g/m^2 and dried. The PET backing was laminated on the adhesive side of the liner and the product was cut in a suitable size to be packed in a sealed package.

Example 2

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	2.5
Oleic acid	1
Styrene·isoprene· styrene block copolymer	25
Saturated alicyclic hydrocarbon (Petroleum resin)	43
Polybutene	8
Liquid paraffin	20
Dibutylhydroxytoluene	0.5
Weight of adhesive	125g/m^2
Backing	PET 3.5μm/paper
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the

method of Example 1, a patch was prepared.

Example 3

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	2
Stearic acid	0.7
Styrene·isoprene· styrene block copolymer	18
Saturated alicyclic hydrocarbon resin (Petroleum resin)	50
Polybutene	5
Liquid paraffin	23.8
Dibutylhydroxytoluene	0.5
Weight of adhesive	90g/m^2
Backing	PET 3.5μm/Unwoven fabric
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the method of Example 1, a patch was prepared.

Example 4

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	3
Oleic acid	0.5
Styrene·isoprene· styrene block copolymer	20
Saturated alicyclic hydrocarbon resin (Petroleum resin)	42
Polybutene	10

Liquid paraffin	23.5
Dibutylhydroxytoluene	1.0
Weight of adhesive	80g/m^2
Backing	PET 12μm
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the method of Example 1, a patch was prepared.

Comparative example 1

The commercially available crystalline type ~~turobuterol~~tulobuterol patch (Trade name: Hokunalin tape prepared by Hokuriku Seiyaku K.K.): ~~Turobuterol~~Tulobuterol: 10 w/w %, 2mg/sheet, size of sheet: 10cm^2

Comparative example 2

By using the same ingredients as in Example 2 provided that in place of the oleic acid 1 w/w %, liquid paraffin 1 w/w % was used, a patch was prepared in the same manner as in the method of Example 1.

Comparative example 3

By using the same ingredients as in Example 2 provided that in place of saturated alicyclic hydrocarbon 43 w/w %, rosin glycerin ester 43 w/w % was used, a patch was prepared in the same manner as in the method of Example 1.

Comparative example 4

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	5.5
Styrene·isoprene· styrene block copolymer	56.8
Diolefin·olefin copolymer	37.7

Weight of adhesive	250g/m^2
Backing	PET 25μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, styrene·isoprene·styrene block copolymer and diolefin·olefin block copolymer were stirred at 150°C. Thereto was added ~~turobuterol~~tulobuterol and the stirred mixture was passed through between release treated PET liner and PET backing during being kept at 110°C and it was rolled under the constant pressure in order to become 250g/m^2 in thickness. The obtained patch was cut in a suitable size to be packed in a sealed package.

This preparation is a highly concentrated, highly contained and soluble type ~~turobuterol~~tulobuterol patch prepared by the method of example (sample 2a) of Japanese Patent No. 2633089.

Comparative example 5

Adhesive	Adhesive layer 5-1 Content (w/w %)	Adhesive layer 5-2 Content (w/w %)
~~Turobuterol~~Tulobuterol	1	5.5
Styrene·isoprene· styrene block copolymer	61.3	56.8
Diolefin·olefin copolymer	37.7	37.7
Weight of adhesive	50g/m^2	200g/m^2
Backing	PET 25μm (Release coating on one side)	PET 25μm (Release coating on one side)
Liner	PET 75μm (Release coating on one side)	PET 75μm (Release coating on one side)

According to the above indications, an adhesive layer 5-1 and an adhesive layer 5-2 were prepared in the same manner as in Comparative example 4. After removing each PET backing, each adhesive surface was

stuck each other to prepare a laminated ~~turobuterol~~tulobuterol patch preparation. The preparation was cut in a suitable size to be packed in a sealed package.

This preparation is a laminated and soluble type ~~turobuterol~~tulobuterol patch prepared by the method of Japanese Patent No. 2633089.

Comparative example 6

Adhesive	Content (w/w %)
~~Turobuterol~~Tulobuterol	5
Isopropyl myristate	40
Styrene·isoprene· styrene block copolymer	38.5
Polyisobutylene	5.5
Saturated alicyclic hydrocarbon resin (Petroleum resin)	11
Weight of adhesive	40g/m^2
Backing	PET 25μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, styrene·isoprene·styrene block copolymer, polyisobutylene and saturated alicyclic hydrocarbon resin were mixed until being homogenous. To the mixture were added and mixed ~~turobuterol~~tulobuterol and isopropyl myristate until being homogenous. The solution was spread on the surface of release treated PET in the amount of 40g/m^2 dried and stuck on PET backing. Thus obtained preparation was cut in a suitable size to be packed in a sealed package.

This preparation was a highly concentrated and soluble type ~~turobuterol~~tulobuterol patch prepared by example 8 of Japanese Patent Publication A 11-228395.

Test 1

A patch of Example 1 (~~turobuterol~~tulobuterol: 2 w/w %, size: 10cm^2) and a commercially available patch of Comparative example 1 were applied to the back of a hair-cut rat respectively. Two, four, eight, ten and twenty four hours later, the blood was taken and ~~turobuterol~~tulobuterol levels in serum were measured by HPLC. Changes of the passage with time of ~~turobuterol~~tulobuterol levels in serum on application of patches of Example 1 and Comparative example 1 were shown in Fig. 1.

From this test result, it was suggested that a patch of Example 1 maintained for a long time ~~turobuterol~~tulobuterol levels in serum as same as the commercialized patch of Comparative example 1, which contains 5 times amount of ~~turobuterol~~tulobuterol as much as the patch of Example 1 has. Therefore, it was shown that the patch of the present invention was a lower concentrated and soluble type patch, and had an ability to control the drug-release for a long time.

Furthermore, according to the disclosure of WO 97/14411, the crystalline type ~~turobuterol~~tulobuterol patch requires to adjust the average particle size of ~~turobuterol~~tulobuterol within 2~20μm, in order to stabilize the drug-release from the patch and its duration. Therefore, due to crystallizing ~~turobuterol~~tulobuterol during adjusting the particle size in the adhesive layer, the ageing process for controlling time and temperature is required.

On the contrast, the patch of Example 1 is a lower concentrated and soluble type ~~turobuterol~~tulobuterol patch and has drug-release ability without containing its crystals. Therefore, it was cleared that the process for preparing for this patch did not require the above mentioned complex ageing processes and the patch could be prepared by a very simple procedure.

Test 2

The skin of abdomen of a hair-cut rat was extracted and fitted on a Frantz-diffusion cell. Phosphate-buffer was used as a reservoir solution and the cell was kept to stir at 37°C during test.

A patch of Example 1, and patches of Comparative examples 2 and 3 were cut in a circle having diameter 13mm (~~Turobuterol~~Tulobuterol of Example 1 and Comparative examples: 2 w/w %, 200μg/cm^2), and the circles fitted on the extracted skin. Small amount of the reservoir solution was from time to time taken and the amount of permeated ~~turobuterol~~tulobuterol was measured by HPLC (Drug permeation test on rat-extracted skin).

Changes of the passage with time of permeated ~~turobuterol~~tulobuterol in case of application of patches of Example 1 and Comparative examples 2 and 3 were shown in Fig 2.

Example 1: ~~turobuterol~~tulobuterol; 2 w/w %, 200μg/cm^2

Comparative example 2 and 3: ~~turobuterol~~tulobuterol; 2 w/w %, 200μg/cm^2

From this test result, the amount of permeated ~~turobuterol~~tulobuterol in regard to the patch of Example 1 was constant in changes of the passage with time. On the other hand, in regard to the patch of Comparative example 2 without containing a higher fatty acid, it showed the tendency that the amount of the permeated drug increased and the duration decreased at a latter half. Furthermore, in Comparative example 3 containing rosin glycerin ester having polarity, the drug permeability greatly decreased.

Test 3

Influence on drug-release by preservation temperature

In order to check the influence on drug-release due to the changes of

preservation temperature, patches of Example 1, Comparative examples 1, 4 and 6 were preserved in incubator kept at 4°C and 40°C respectively for 3 weeks, and then the temperature was adjusted to room temperature. In the same manner as Test 2 the drug permeation test on the skin extracted from rat was carried out.

In case of application of patches of Example 1, Comparative examples 1, 4 and 6, changes of the passage with time of the permeation of ~~turobuterol~~tulobuterol were shown in Fig. 3. The drug-permeation rate due to changes of preservation temperature was shown in Table 1.

Example 1: ~~turobuterol~~tulobuterol; 2 w/w %, 200μg/cm^2

Comparative example 1: ~~turobuterol~~tulobuterol; 10 w/w %, 200μg/cm^2 (Crystalline type ~~turobuterol~~tulobuterol patch)

Comparative example 4: ~~turobuterol~~tulobuterol; 5.5 w/w %, 1375μg/cm^2 (Highly concentrated, highly contained and soluble type ~~turobuterol~~tulobuterol patch)

Comparative example 6: ~~turobuterol~~tulobuterol; 5 w/w %; 200μg/cm^2 (Highly concentrated and soluble type ~~turobuterol~~tulobuterol patch)

Table 1

Rate of drug permeated amount due to changes of preservation temperature on each sample

Test example	Example 1	Comparative example 1	Comparative example 4	Comparative example 6
Rate of permeation	89 %*	65 %	162 %	44 %

*Example of calculation: {permeation amount of Example 1 (4°C) (8 hr)} / {permeation amount of Example 1 (40°C) (8 hr)} × 100

From this test result, it was shown that the drug permeated amount on a patch of Example 1 was constant and hardly influenced by changes of

preservation temperature.

On the other hand, it was shown that the group of Comparative examples was apt to receive the influence by the changes of preservation temperature.

This fact suggested that due to changes of preservation temperature, the rate of crystals and dissolved portion in the adhesive was changed and due to the high concentration of the drug, the degree of saturation in the adhesive was changed, or since the drug was easy to separate from the constituents of the additive, it was possible that the amount of permeation of the drug was greatly changed up and down.

Test 4

Influence on drug-release by preservation term

In order to see the influence on drug-release by preservation term, by using two kinds of patches of Example 4, which was prepared 12 hours before and which was preserved for 2 months at room temperature, and two kinds of patches prepared by sticking layers 5-1 and 5-2 in Comparative example 5, which was prepared 12 hours before, and which was preserved for 2 months at room temperature, in the same manner as in Test 2, the drug permeation test on the skin extracted from rat was carried out. In regard to patches of Comparative example 5, the 5-1 layer side which was lower in the drug concentration was applied to the skin.

Changes of the passage with time of permeated ~~turobuterol~~tulobuterol in case of application of patches of Example 4 and Comparative example 5 were shown in Fig 4.

Example 4: ~~turobuterol~~tulobuterol; 3 w/w %, 240 μg/cm^2

Comparative example 5: (adhesive layer 5-1) ~~turobuterol~~tulobuterol; 1 w/w %, 50 μg/cm^2 + (adhesive layer 5-2) ~~turobuterol~~tulobuterol; 5.5w/w %, 1108μg/cm^2 (laminated patch)

From this test result, it was shown that a patch of Example 4 was constant in drug permeation amount with changes of the passage with time.

On the other hand, in regard to a patch of Comparative example 5, the drug permeation amount was increased with changes of the passage with time. Even if the adhesive had the higher drug concentration, the drug permeation amount was controllable by sticking the layers having the lower drug concentration, but it was considered that the transfer between adhesive layers occurred and the concentration of the drug was averaged during a long time and therefore the control of the drug-release was injured.

INDUSTRIAL APPLICABILITY

The patch of the present invention is prepared by dissolving ~~turobuterol~~tulobuterol in the lower concentration in an adhesive layer and thereto adding a higher fatty acid, a rubber, an adhesive agent and a plasticizer in a suitable amount respectively, can easily control the ~~turobuterol~~tulobuterol release pattern and is excellent in changes of the passage with time of release pattern.

Furthermore, according to the present invention, essential physical properties on a patch such as adhesivity and shape retention is suitably adjusted and by simplifying the method for preparation, the patch of the present invention has following advantages comparing with the known ~~turobuterol~~tulobuterol-patch:

(1) Despite fact that the content of ~~turobuterol~~tulobuterol is less, the effect can be optimized according to the therapeutic object as the patch of the present invention shows sufficient ~~turobuterol~~tulobuterol release amount and it is possible to widely and simply control the ~~turobuterol~~tulobuterol release amount.

(2) The adjustment of essential properties as a patch is possible together with controlling the release amount and releasing pattern of

~~turobuterol~~tulobuterol. Therefore, it becomes possible to provide a patch which is therapeutically effective and has physical properties suitable to the skin condition.

(3) During preservation, the influence by changes of circumstances is less and the quality is stably kept for a long term.

(4) The preparation method is very simple and practical.

ABSTRACT

A patch containing ~~turobuterol~~tulobuterol in the low concentration and having the stable release-controllability, prepared by laminating an adhesive layer consisting of a rubber, an adhesive resin and a plasticizer on a backing, wherein 1 to 4 w/w % of ~~turobuterol~~tulobuterol in the lower concentration as an active ingredient and 0.1 to 3 w/w % of a higher fatty acid as a drug-releasing controlling agent are contained in the adhesive layer.